Depression alters maternal extended amygdala response and functional connectivity during distress signals in attachment relationship

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Abstract

Maternal attachment-related parenting behaviors require mothers to regulate self-related and child-related distress. Emotion regulation is, in turn, influenced by maternal mood and personal developmental history. In the current study we examined how depressive mood may alter maternal limbic system function and functional connectivity underlying defensive and hedonic motivations. Twenty nine mothers were recruited to undergo a baby-cry task during a functional magnetic resonance imaging (fMRI) scan. Based on self-reported depression symptoms and clinical interview, the participants were grouped as healthy controls (n = 15) and currently depressed (n = 14). In the baby-cry task, 30s-long auditory stimuli of baby-cry sounds were presented to simulate four conditions: generic baby-cry (Just-Listen), baby-cry as if it were their own child's cry (Your-Baby), baby-cry as if it were themselves (Self), and matched control sounds (Noise). Depressed mothers, as compared to healthy controls, showed greater Self versus Just-Listen responses in left extended amygdala and decreased functional coupling between this left extended amygdala as the seed and nucleus accumbens (NAc) in self-oriented (Self versus Just-Listen) and child-oriented (Your-Baby versus Just-Listen) distress signals. Moreover, the extended amygdala's differential functional connectivity with dorsomedial prefrontal cortex (dmPFC) during the Your-Baby versus Self was increased for depressed mothers and decreased for healthy controls. Thus, depression may affect mothers by increasing baby-cry threat responses and dysregulating associations between threat and heathy child-oriented parenting motivations. These results are discussed in the context of attachment and self-psychology.

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Keywords

Introduction

Depression in adulthood has been linked to negative childhood experiences with parents, whether from outright abuse and neglect [1] or perceived parental coercion and criticism that may be internalized through the attachment relationship [2]. It has been suggested that depression and anxiety manifest symptoms of low self-esteem due to inadequate development of self, which may stem from lack of secure attachment development [3]. Low self-esteem and insecure attachment with diminished self-image as perceived by others is also known to be related to non-parent caregiver burnout [4]. When a mother under the influence of early-life negative attachment-related experiences develops depression with excessive self-criticism and low self-esteem, the mother's child can also be adversely affected [5–8]. Depressed mothers manifest higher levels of negative parenting behaviors such as hostile/coercive behaviors, and lower levels of engagement and positive social interactions with their child [9, 10].

Thus, maternal depression reflects excessive negative affect toward self and others in attachment relationships (such as between parent and child). It originates during the mother's own childhood when she was attempting to develop a cohesive relationship with her primary caregiver. From a psychodynamic perspective, children develop a representation of a primary caregiver, as a self-object, and subsequently develop effective control of the caregiver self-object similar to developing control of his or her body, before developing a representation of self later on. Failure to develop a cohesive self can result from an incoherent relationship between the representations of each child's self and self-object [11]. Without such cohesion, insecure attachment, low self-esteem and, eventually, symptoms of depression may develop [3]. Indeed, insecure attachment and excessive reassurance seeking have been associated with depressive symptoms [12]. These phenomena suggest potential interactions among negative self-representation, insecure relationship with other key attachment figures and depression.

We postulated that maternal depression plays a role in maternal parenting behaviors by affecting how mothers respond to representations of self and others when encountering child's distress signals. Indeed, mothers with higher dispositional personal distress tend to react to their child's distress with more negative affect [13]. Distress signals can trigger depressed mothers' own negative autobiographical memories from childhood [14]. However, self-reported measures may not capture the relationship between self-oriented and child-oriented emotional responses in mothers because maternal negative responses to child's distress may not be readily recognized by mothers as stemming from their own attachment and self-esteem development. We resorted to neuroimaging methods, using baby-cry as stimuli in a functional magnetic resonance imaging (fMRI) study, to probe how maternal brain responses to distress signals can be affected by depression in this study, focusing on

motivation-related extended amygdala, including the threat-processing central amygdala, sublenticular extended amygdala, bed nucleus of the stria terminalis, reward-processing nucleus accumbens (NAc), and dorsomedial prefrontal cortex (dmPFC) related to representing mental states of others [15].

Certainly, baby-cry is a primal distress signal that every infant makes to elicit caregiving from parents. For mothers, hearing baby-cry may elicit a myriad of implicit and explicit emotional states, memories and behavioral responses under the influence of their own attachment development [16]. Using baby-cry stimuli, brain imaging studies have begun to show that brain physiology of mothers is a function of depressive symptoms [17]. For example, response to baby-cry in the lenticular nucleus (part of threat processing extended amygdala) and left medial prefrontal cortex (PFC) was proportional to anxious intrusive thoughts and depression respectively among healthy mothers during early postpartum period [18]. Functional connectivity among these social and emotional brain circuits has also been linked with stress and psychopathology [19, 20]. Specifically, mothers with diagnoses of postpartum depression, as compared to healthy controls, have shown decreased functional connectivity between amygdala and paralimbic cortex while viewing fearful and threatening faces [21]. In accord, depression and trait anxiety have been demonstrated to be inversely related to amygdala-insula connectivity while mothers attended to positive baby pictures [22]. Furthermore, in response to own vs. generic baby-cry among postpartum depressed versus non-depressed mothers, caudate and NAc activity was reduced at 15–18 months postpartum [23]. Finally, major depression when not occurring in the postpartum seems to alter the functional connectivity related to the limbic system [24, 25].

The effects of depression on maternal brain responses to distress signals from self and others in attachment relationships have not previously been addressed. In order to probe maternal self-oriented and other-oriented responses to distress signals in attachment relationship, we devised an individually personalized, identity-dependent baby-cry task. We presented baby-cry stimuli with instructions to perceive them according to three distinct identities, by instructing each participant to imagine that the baby-cry stimulus was coming from (1) an unknown baby, (2) her own child, and (3) herself - as if baby-cry had been recorded when the she was a baby crying. We conceptualize that these three conditions correspond to distinct aspects of a mother's response to baby-cry, respectively: (1) perceiving the cry as a general distress signal [26, 27]; (2) perceiving the cry as a signal reflecting her own personal responsibility and attachment to her own baby [28, 29], and (3) perceiving the cry as a signal that activates her own personal history of distress, perception of their own experience of maternal care, and quality of attachment security [30, 31].

Thus, we postulated that depressive mood will "color" maternal brain responses to baby-cry in the according to the three tasks. Depression increases general irritability [9], influences maternal perception of her child [32, 33] and relates to early childhood maltreatment with persisting self-oriented negative thoughts and emotions [2]. Finally, we expect that the contrast between child-oriented and self-oriented baby-cry (Your-Baby versus Self) will reveal brain mechanisms through which each mother relates to her child as an attachment figure beyond self-oriented concern, which is a hallmark of empathy [34, 35]. Maternal depression may alter brain responses in Your-Baby versus Self contrast, in accord with

maladaptive development of self objects [3]. Indeed, amygdala-related functional connectivity during Your-Baby versus Self has been related to changes in parenting stress [36], so we also hypothesize that maternal depression would influence functional connectivity of the extended amygdala.

Methods

Procedures

Participants were recruited from community health clinics, primary care clinics, and University of Michigan hospitals. All participants were mothers living with at least one biological child. Participants underwent a brief psychiatric phone screener (2 screening questions from SCID interview for past and/or current depression [37] and completed the Beck Depression Index (BDI) [38], among other questionnaires outside the scope of this report. The participants then underwent a functional magnetic resonance imaging scan. All procedures were approved by University of Michigan's Institutional Review Board.

Participants

According to the current BDI scores (cutoff = 11) and the diagnostic history obtained in the screening interview, we sorted the participants (n = 29) into two groups, Healthy Control (n = 15) and Currently Depressed (n = 14). As reported in Table 1, the two groups did not significantly differ in the number of participants, age, number of children per mother, and the age of their youngest child. The BDI score was significantly different between groups.

Functional Magnetic Resonance Imaging (fMRI) Task

Baby-Cry Task—The fMRI task utilized auditory stimuli selected from our in-house battery created previously, which has been used in prior work [23, 31, 39–44]. The baby-cries were recorded from three two-week old infants during a diaper change and organized as 30 second long stimuli of matching in intensity. Each of these three infants' baby-cri stimuli was used in each of the following conditions, when mothers were instructed to listen to the baby-cry stimuli using different frames of reference: 1) passive listening to baby-cry (Just-Listen), 2) listening to baby-cry and imagining that their own child was crying (Your-Baby), 3) listening to baby-cry and imagining that the participants themselves were the crying baby (Self), and 4) passive listening to control sound (Noise). In this way, the protocol provokes responses according to the perception of different aspects of baby-cry. The baby-cry stimuli, each preceded by a descriptive primer of the conditions, were presented randomly in blocks of 30 second, with one trial of baby-cry or control sound per block. There were two runs of 4.5 min/run, wherein there were three blocks for each of the four conditions. Each block was separated by a 10-sec period during which only background scanner noise could be heard and a cross visually presented for fixation. This baby-cry task has been used to study non-mothers as a function of early childhood poverty [45] and mothers whose child was more than 12 months old [36].

Pre-scan Ratings on Auditory Stimuli Used in the fMRI Task

Immediately before the scanning, participants listened to all 30 second auditory stimuli that would be used in the fMRI task and answered questions on a 5-point Likert scale

immediately after listening to each stimulus: For baby-cry, we asked: "What is the intensity of this cry?" (1 = very low, 3 = middle, 5 = very strong) and "How annoying is this cry?" (1 = Not at all, 3 = moderate, 5 = very annoying), and "If this crying baby were in the same room with you, how much would you like to move closer to or away from this baby" (1= very much away, 3 = neutral, 5 = very much closer). For Noise stimuli, we asked: "What is the intensity of this noise? (1 = very low, 3 = middle, 5 = very strong) and "How annoying is this noise?" (1 = Not at all, 3 = moderate, 5 = very annoying).

Functional and Structural Magnetic Resonance Imaging

During the fMRI scanning session, each participant was positioned in a supine orientation with her head positioned in a head coil. The task was presented with E-Prime (PST, Inc., Pittsburgh, PA), via a goggle system and Nordic NeuroLab audio system. Behavioral responses were recorded by a button glove attached to the participant's right hand and linked to the E-Prime system. All fMRI scanning sessions were performed with a 3.0 Tesla Philips magnetic resonance imaging scanner using a standard 8-channel radiofrequency SENSE head coil with the following acquisitions: (1) A high-resolution T1 scan was acquired to provide precise anatomical localization (TR of 9.8ms, TE = 459 ms, FA = 8°, FOV of 256 mm, slice thickness of 1.0 mm, 180 slices with 288×288 matrix per slice). (2) Two runs of T2*-weighted EPI sequence with BOLD (blood oxygenation level dependent) contrast (190 frames per run, TR = 2000 ms, TE = 30 ms, FA = 90°, FOV = 220 mm, 42 contiguous axial slices, slice thickness = 2.8 mm with 64×64 matrix per slice, voxel size = $3.44 \times 3.44 \times 2.8$ mm^3) were acquired for whole-brain fMRI BOLD signal measures during the experimental task.

Data Processing and Analysis—Functional MRI data were pre-processed and analyzed using statistical parametric mapping software (SPM8; Welcome Department of Imaging Neuroscience, London UK). Five images at the beginning of each fMRI run were discarded to account for magnetic equilibrium. Slice timing correction was performed using a middle slice as reference (slice 21). After slice time correction, images within each run were realigned to the mean image of the first run to correct for movement. Realigned functional and structural images were spatially normalized using DARTEL methods in SPM8. The normalized functional images were re-sliced to 2×2×2mm voxels. Images were then spatially smoothed using a Gaussian filter with a full-width half-maximum value of 8mm. Following pre-processing, participant-specific first-level fixed-effect models were constructed with a matrix of regressors modeling each trial type (Just-Listen, Your-Baby, Self, and Noise). Each individual participant's contrasts of interest at the first level were submitted to second-level random-effect General Linear Models (GLMs). A one-way ANOVA model was used to examine the differences among the three groups. A set of structures were used as a priori regions of interest (ROIs) to examine the neural responses, including extended amygdala [46] for threat-related processing and NAc for reward related processing. In addition to these limbic areas, a ROI in dorsomedial prefrontal cortex (dmPFC) as a sphere of 12mm radius centered at MNI coordinates (0, 56, 20) was selected according to automated meta-analysis using "social cognition" and "mentalizing" as keywords on Neurosynth [47]. The results reported here are clusters with the peak voxel surviving the small volume correction in these ROIs with family-wise error (FWE) < 0.05,

with the bar charts in the figures plotting the estimated marginal means and standard errors after accounting for the mothers' youngest child's age.

Results

Self-reported ratings on the auditory stimuli

Participant ratings of auditory stimuli (intensity and negative valence for noises and cries, and positive valence for cries only) before the scanning were submitted to a GLM, using Groups (Healthy and Depressed) as a between-subject independent variable and the age of the youngest child as a covariate. There were no significant main effects of Groups on any of the ratings. See Table 2.

fMRI results

Group differences in differential neural responses—The main effects of Groups, Depressed versus Healthy, were examined in four contrasts of interest: (1) Just-Listen versus Noise, to examine the neural responses to a generic baby-cry distress signal, (2) Your-Baby versus Just-Listen, to examine the neural responses specific to each mother's own child's distress signal, (3) Self versus Just-Listen, to examine the neural responses specific to each mother's self-oriented distress, and (4) Your-Baby versus Self, to examine whether neural responses differ between other-oriented and self-oriented baby-cry distress, which is assumed to reflect responses specific to the representation of child versus self in social cognition brain areas. There were no Depression versus Healthy Group main effects on the contrast of Just-Listen > Noise, Your-Baby > Just-Listen, or Your-Baby > Self. The groups were different in the Self > Just-Listen in the left extended amygdala, which were significantly greater than zero in the Depressed mothers and significantly less than zero in the Healthy mothers. The results are summarized in Table 3 and Figure 1.

Group differences in differential functional connectivity—To further examine the group differences in functional connectivity, we used the left extended amygdala, that showed significant group differences in Self > Just-Listen, as seed for a generalized physiological psychological interaction (gPPI) analysis [48]. In a one-way ANOVA model, we found that there were significant group differences (Healthy > Depressed) in the left extended amygdala's differential functional connectivity with the right NAc in the contrast of Your-Baby > Just-Listen and with the left NAc in the contrast of Self > Just-Listen. Moreover, we found significant group differences (Depressed > Healthy) in the left extended amygdala's differential functional connectivity with the dmPFC, which is related to social cognition and representing another person's mental states [15]. While Healthy mothers down-regulated the functional connectivity between the left extended amygdala and dmPFC during Your-Baby versus Self, Depressed mothers up-regulated the functional connectivity between these two regions. These results are summarized in Table 4 and Figure 2.

Discussion

The results of this study provide preliminary evidence that maternal depression alters neural responses to baby-cry distress signals depending on which perspective mothers take when

perceiving baby-cry distress signals. We did not find any significant effects of maternal depression on arousal or annoyance ratings of the generic baby-cry condition, nor did we find any depression effects on neural responses to generic baby-cry (Just-Listen) with reference to control sound (Noise). Thus, we did not find evidence supporting the notion that depressed mothers are simply more irritated or annoyed by generic baby-cry distress signals. Similarly, we did not find any significant depression effects on the differential neural activations to own baby-cry (Your-Baby) versus a general baby-cry (Just-Listen). Thus, we did not find evidence supporting the notion that the levels of depression in our sample altered maternal responses to their own child's distress.

However, we found significant maternal depression effects on the differential neural activations of self-distress (Self) versus a generic distress (Just-Listen) in the extended amygdala (Figure 1). Specifically, while the extended amygdala's responses were decreased in the Self condition as compared to Just-Listen in Healthy Controls, they were increased in the currently Depressed mothers. These results are consistent with the neuroimaging literature showing the role of extended amygdala in threat reactivity and the development of persistent anxiety and depression [46, 49]. Given the roles of the extended amygdala in threat processing [50] and personal distress during perceived failures in parenting-related decision-making [51], the current findings suggest that the self-oriented distress aspect of baby-cry perception may be more threatening for depressed mothers than healthy mothers.

Furthermore, using the left extended amygdala as the seed in differential functional connectivity (gPPI) analyses, we found that Depressed mothers showed diminished functional connectivity between the NAc and the extended amygdala, as compared to Healthy Controls, in both Your-Baby versus Just-Listen and Self versus Just-Listen contrasts (Figure 2A, 2B). Given the roles of extended amygdala for threat processing and the NAc for reward processing, the functional connectivity between these regions during own baby-cry distress may reflect a biological mechanism responsible for the difficulties of depressed parents to integrate baby-cry distress signal processing with the reward processing required for sensitive parenting behaviors, which are diminished in maternal depression [52]. Perhaps healthy mothers, as compared with depressed, are more able to activate their NAc during baby-cry distress signaling to motivate caring behaviors for their baby or themselves.

Moreover, we found that functional connectivity between the extended amygdala and dmPFC was greater among Depressed mothers than healthy controls during child versus self-oriented distress responses (Your-Baby versus Self) (Figure 2C). The dmPFC is a key brain area in the representation of others in social cognition such as while mentalizing other's states [15, 53] and resting-state functional connectivity between dmPFC has been found to be stronger in depressed patients than healthy controls [54]. These results suggested that child's distress signals may have triggered a process that connects representations of self and other with emotional values that is consistent with the literature on self-psychology [11, 55]. In contrast to Depressed mothers, healthy mothers may be more able to inhibit the association of threat-related negative emotion processing in the extended amygdala with representations of their own child in the dmPFC.

The following limitations of the current study should be noted. Firstly, the modest sample size prompts caution and requires replication to generalize findings. Secondly, we did not include mothers with severe depression, in which different mechanisms may operate. Thirdly, because this study did not include fathers, who are themselves the subject of a growing literature [56, 57], parent sex effects were not examined. Lastly, this study lacks more comprehensive psychiatry diagnostic tools, more detailed assessments of parental thoughts and behaviors and coded measurements of actual parent behavior and child outcomes [58] to determine transgenerational effects of maternal depression.

Taken together, we found preliminary evidence that depression affects how mothers process the motivationally salient distress signal of baby-cry. Depression heightens reactivity for self-oriented distress in the extended amygdala - a key limbic threat processing region, when relating to the distress signals as self-oriented. Furthermore, currently Depressed mothers exhibit decreased functional connectivity between the extended amygdala and NAc, which could mean that their threat-processing extended amygdala is less sensitive to positive motivational signals from NAc. Depression also increases functional connectivity between the extended amygdala and dmPFC. This may be interpreted as extended amygdala projecting excessive self-oriented distress towards the child as represented in dmPFC. Conversely for the same conditions, healthy mothers showed inhibited extended amygdala reactivity to self-oriented distress signals, increased connectivity with motivation signaling and inhibited functional connectivity with dmPFC suggesting inhibiting association of threat processing and child representation. These findings suggest a potential neural mechanism rooted in self psychology underlying depressed mothers' excessive negative affects towards their offspring [9].

Due to the excessive association between maternal negative emotions and the child, depressed mothers may tend to project their own distress toward the child, as part of the struggles of their vulnerable self-concept. These struggles may stem from the pathological process of insecure attachment development, specifically, related to incoherent relationships between the representations of self and self-objects or others in attachment relationships [11]. Consistent with the notion that child-oriented empathy is a hallmark of mental health [35], the results of this paper suggest that extended amygdala responses to distress signals may play a pivotal role in the difference between healthy and pathological responses to distress signals in attachment relationships. Specifically, depressed mothers may benefit from therapeutic strategies aimed at weakening the association between maternal threat-related negative emotions and representations of others such as child, spouse, and other key attachment figures.

Acknowledgments

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Research Highlights

- Maternal neural responses to distress signals (baby-cry) were examined in three distinct aspects of perceptions: general arousal, child-oriented, and self-oriented - in mothers with depressive moods and healthy controls. Mothers with depressive mood showed greater self-oriented neural responses in left extended amygdala, as compared to healthy controls.

- Mothers with depressive mood showed decreased functional connectivity between the extended amygdala and nucleus accumbens during self-oriented and child-oriented responses to distress signals, while healthy controls showed results in the opposite direction.

- Mothers with depressive mood showed increased functional connectivity between the left extended amygdala and dorsomedial prefrontal cortex (dmPFC) during child-oriented versus self-oriented responses to distress signals, while healthy controls showed results in the opposite direction.

Self > Just-Listen

y = 4

Left Extended Amygdala
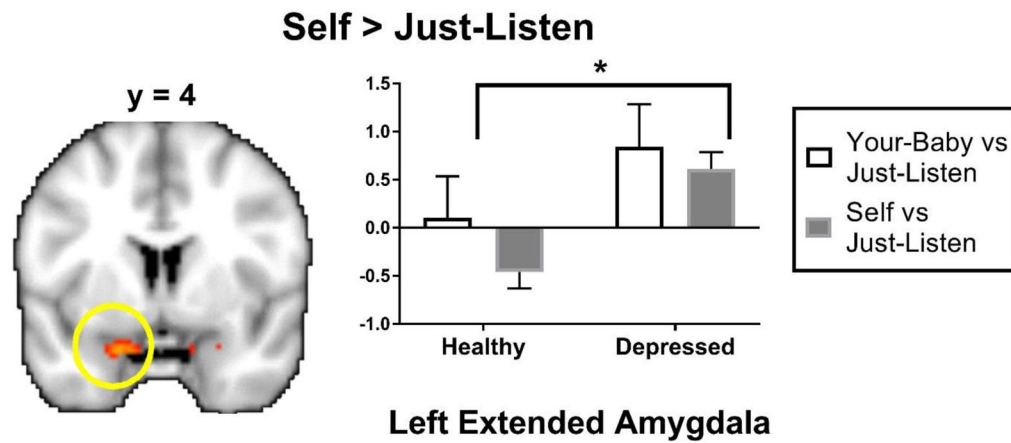
Figure 1.
The group differences among Healthy, Remitted, and Depressed mothers in Self > Just Listen differential neural responses were found in the left extended amygdala, surrounded by a yellow circle. The bar chart of the parameter estimates and standard error is presented. The asterisk (*) indicates the significant group effect on Self versus Just-Listen, while Your-Baby versus Just-Listen results are also presented.
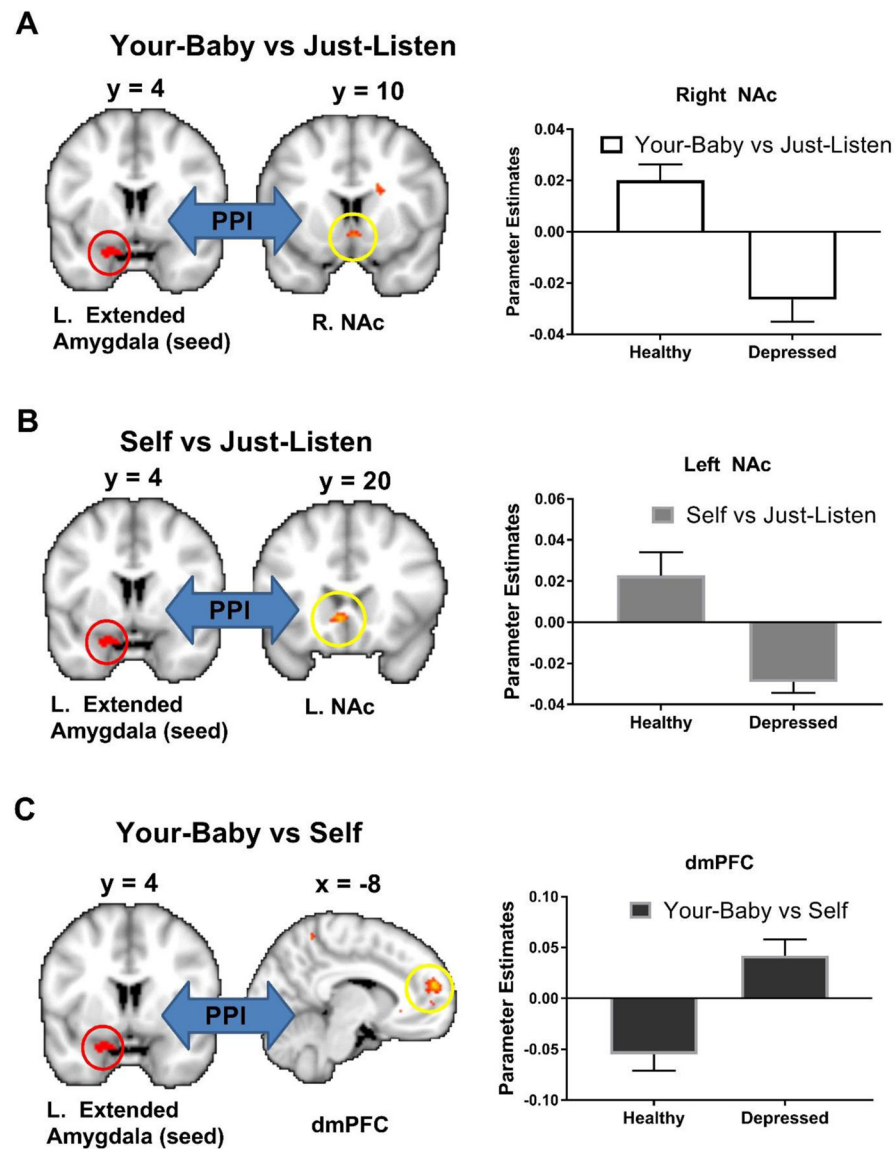
Figure 2.
Using the left extended amygdala as the seed (in red circle) in the generalized physiological-psychological interaction (gPPI) analysis, the group differences among Healthy, Remitted, and Depressed mothers were found in the Your-Baby > Just-Listen differential functional connectivity between the seed and right nucleus accumbens (A), in the Self > Just-Listen differential functional connectivity between the seed and left nucleus accumbens (B), and in the Your-Baby > Self differential functional connectivity between the seed and dorsomedial prefrontal cortex (C). The bar charts of the parameter estimates and standard error in the clusters surrounded by yellow circles are presented next to the clusters' images.

Table 1

Participant characteristics according to Healthy and Depressed groupings.

	Healthy	**Depressed**	**Group Difference**
N	15	14	*n.s.*
Age	34.46 (±1.99)	29.66 (±2.07)	*n.s.*
Number of children	1.67 (±0.21)	1.86 (±0.21)	*n.s.*
Age of the youngest child	3.90 (±0.52)	2.43 (±0.54)	*n.s.*
BDI	1.33 (±1.79)	13.8 (±1.38)	*p = 0.001*

Table 2

Participant self-reported ratings on auditory baby-cry

	Healthy	Depressed	Group Difference
Arousal Rating			
Noise	2.56 (±0.26)	2.79 (±0.25)	*n.s.*
Cry	3.80 (±0.18)	3.65 (±0.17)	*n.s.*
Negative Valence Rating			
Noise	2.58 (±0.32)	2.88 (±0.26)	*n.s.*
Cry	2.63 (±0.28)	3.06 (±0.27)	*n.s.*
Positive Valence Rating			
Cry	3.64 (±0.32)	3.64 (±0.30)	*n.s.*

Table 3

Main effects of health and depressed participant groupings on brain Responses to baby-cry stimuli

Main Effects of Groups (Healthy and Depressed) on Neural Responses						
		MNI Coordinates			No. of Voxels	Z score
Brain Region	**Side**	**X**	**Y**	**Z**		
Just-Listen versus Noise						
None						
Your-Baby versus Just-Listen						
None						
Self versus Just-Listen						
Extended amygdala	L	−18	4	−22	83	3.33

Table 4

Main effects of healthy and depressed participant groupings on functional connectivity during baby-cry stimuli.

Main Effects of Groups (Healthy and Depressed) on Functional Connectivity						
		MNI Coordinates				
Brain Region	**Side**	**X**	**Y**	**Z**	**No. of Voxels**	**Z score**
Just-Listen versus Noise						
None						
Your-Baby versus Just-Listen						
Seed: Left extended amygdala						
Nucleus accumbens	R	2	10	−8	33	3.56
Self versus Just-Listen						
Seed: Left extended amygdala						
Nucleus accumbens/caudate	L	−4	24	−4	89	3.57
Your-Baby versus Self						
Seed: Left extended amygdala						
dmPFC	L	−8	54	20	168	3.42